General

Guideline Title

Evidence-based guideline: clinical evaluation and treatment of transverse myelitis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011 Dec 13;77(24):2128-34. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (I-IV) are provided at the end of the "Major Recommendations" field.

In patients with suspected transverse myelitis (TM), distinction between acute complete transverse myelitis (ACTM) or acute partial transverse myelitis (APTM) may be considered useful to determine the etiology of TM and the risk for relapse (more common in APTM) (Level C).

Age and gender may be considered useful to determine etiology in a patient presenting with TM syndrome, with spinal infarcts seen more often in older patients and more female than male patients having TM due to multiple sclerosis (MS) (Level C). Due to considerable overlap between groups, patient demographic characteristics are not definitive in establishing the cause of myelopathy.

There is insufficient evidence to support or refute the usefulness of ethnicity to determine the cause of a subacute myelopathy (Level U).

Brain magnetic resonance imaging (MRI) characteristics consistent with those of MS may be considered useful to predict conversion to MS after a first episode of partial TM (Level C).

Longer spinal lesions extending over more than 3 vertebral segments may be considered useful in determining neuromyelitis optica (NMO) vs MS (Level C).

NMO-immunoglobulin G (IgG) antibodies should be considered useful to determine the cause of TM in patients presenting with clinical features of ACTM (Level B).

Cerebrospinal fluid (CSF) examination for cells and oligoclonal bands (OCBs) may be considered useful to determine the cause of the TM syndrome (Level C).

The presence of NMO-IgG antibodies (aquaporin-4–specific antibodies) should be considered useful in determining an increased risk of TM recurrence (Level B).

Plasma exchange may be considered in patients with TM who fail to improve after corticosteroid treatment (Level C). Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses (Level C). There is insufficient evidence to support or refute the efficacy of other therapies (Level U).

Definitions:

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Classification of Evidence for Therapeutic Interventions

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.
**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Classification of Evidence for Diagnostic Tests

Class I: A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient's clinical status. Study results allow calculation of measures of diagnostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared to a broad spectrum of controls or a cohort study where a broad spectrum of persons with the suspected condition where the data was collected retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III: A case control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Classification of Evidence for Prognostic Articles

Class I: A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III: A case control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Clinical Algorithm(s)

None available

Scope

Disease/Condition(s)

Transverse myelitis (TM)

Guideline Category

Assessment of Therapeutic Effectiveness

Diagnosis

Evaluation

Management

Risk Assessment

Technology Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurology

Pathology

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the evidence for diagnostic tests and therapies for transverse myelitis (TM) and make evidence-based recommendations

Target Population

Patients with transverse myelitis (TM)

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment

1. Evaluation of demographic features (age, gender, ethnicity)
2. Evaluation of clinical features (e.g., distinction between acute complete transverse myelitis [ACTM] or acute partial TM [APTM])
3. Brain and spinal magnetic resonance imaging
4. Laboratory evaluations: cerebrospinal fluid (CSF) leukocyte count, analysis of serum neuromyelitis optica immunoglobulin G (NMO-IgG) antibodies, CSF analysis for oligoclonal bands, presence of CSF pleocytosis

Management/Treatment

1. Plasma exchange
2. Rituximab
3. High-dose intravenous methylprednisolone, mitoxantrone, and other immunosuppressive therapies (note: these therapies were considered, but there was insufficient evidence regarding efficacy to recommend them)

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Efficacy of therapy in alleviating transverse myelitis (TM) attacks
- Effectiveness of therapy in preventing future TM attacks

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline sought to answer the following questions regarding patients with myelopathy: which demographic, clinical, radiographic, and laboratory features are useful:

1. To distinguish transverse myelitis (TM) from other causes of acute and subacute noncompressive myelopathy?
2. To determine the cause of the myelitis?
3. To identify patients at increased risk for recurrence?

For patients with TM, which therapies

4. Alleviate acute attacks?
5. Prevent future attacks?

A literature search of Medline was performed for relevant articles published from 1966 to March 2009, using the following key words: myelitis, transverse myelitis, Devic disease, neuromyelitis optica, diagnosis, prognosis, outcomes, MRI, and treatments. The search was limited to reports in humans and abstracts available in English. Subheadings were applied as appropriate. The exact search strategy employed is described in Appendix e-1 of the Data Supplement in the original guideline document. A secondary search of review articles was done to find any missed citations.

The guideline developers reviewed all abstracts; the full text of potentially relevant articles was subsequently reviewed by at least 2 committee members. The guideline developers excluded review articles and case reports.

Number of Source Documents

The literature search yielded 136 articles. All articles were reviewed in their entirety. Sixty-five articles met inclusion criteria.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence for Therapeutic Interventions

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

The following are also required:

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    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
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measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

At least 2 committee members independently rated each article for its class of evidence using the American Academy of Neurology (AAN) diagnostic (questions 1 and 2), prognostic (question 3), or therapeutic (questions 4 and 5) classification of evidence schemes (see the "Rating Scheme for the Strength of the Evidence" field). Differences between reviewers were resolved through discussion with a third reviewer.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendations were formulated and linked to the strength of the evidence using the scheme described in the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields.

This guideline was approved by the Therapeutics and Technology Assessment Subcommittee on November 13, 2010; by the Practice Committee on May 11, 2011; and by the AAN Board of Directors on October 14, 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Increased accuracy of diagnostic tests and improved therapies for people with transverse myelitis (TM)

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011 Dec 13;77(24):2128-34. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Dec 13

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology

Guideline Committee

Therapeutics and Technology Assessment Subcommittee

Composition of Group That Authored the Guideline

Guideline Authors: T.F. Scott, MD; E.M. Frohman, MD, PhD; J. De Seze, MD; G.S. Gronseth, MD, FAAN; B.G. Weinshenker, MD

Therapeutics and Technology Assessment Subcommittee Members 2009–2011: Janis M. Miyasaki, MD, MEd, FAAN (*Co-Chair*); Cynthia L. Harden, MD (*Co-Chair*); Richard M. Camicioli, MD; Terry D. Fife, MD, FAAN; Jonathan Hosey, MD, FAAN (Ex-Officio); Cheryl Jaigobin, MD; Barbara S. Koppel, MD, FAAN; Jason Lazarou, MD; Alexander Rae-Grant, MD; William H. Theodore, MD, FAAN

Financial Disclosures/Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

Dr. Scott has received funding for travel or speaker honoraria from, served on the speakers' bureaus and scientific advisory boards of, and performed consultation work for Acorda Therapeutics Inc., Avanir Pharmaceuticals, Biogen Idec, Novartis, and Teva Pharmaceutical Industries Ltd.; served as an associate editor for *BMC Neurology*; and has received research support from Biogen Idec, National Multiple Sclerosis Society, Novartis, Pittsburgh Foundation, and Teva Pharmaceutical Industries Ltd. Dr. Frohman has received funding for travel and/or speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Genzyme Corporation, Abbott, Acorda Therapeutics Inc., and Bayer Schering Pharma; has served on speakers' bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Athena Diagnostics; and has served as a consultant for Biogen Idec, Teva Pharmaceutical Industries Ltd., Athena Diagnostics, Inc., Acorda Therapeutics Inc., and Abbott. Dr. de Seze serves on scientific advisory boards for and has received honoraria from Biogen Idec, LFB, Merck Serono, sanofi-aventis, and Bayer Schering Pharma; and serves on the editorial board of *Revue Neurologique*. Dr. Gronseth serves as an editorial advisory board member of Neurology Now, serves on a speakers' bureau for Boehringer Ingelheim, and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. Weinshenker serves on data safety monitoring boards for Novartis and Biogen Idec; serves on the editorial boards of the *Canadian Journal of Neurological Sciences*, the *Turkish Journal of Neurology*, and *Multiple Sclerosis*; has received research support from Genzyme Corporation and the Guthy-Jackson Charitable Foundation; and receives license royalties from RSR Ltd. for a patent re: Aquaporin-4 associated antibodies for diagnosis of neuromyelitis optica.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

Availability of Companion Documents

The following are available:

- Clinical evaluation and treatment of transverse myelitis. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2011. 2 p. Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site .
- Clinical evaluation and treatment of transverse myelitis. Case presentation. St. Paul (MN): American Academy of Neurology. 2011. 5 p. Available in PDF from the AAN Web site .
- Clinical evaluation and treatment of transverse myelitis. Slide presentation. St. Paul (MN): American Academy of Neurology. 2011. 56 p. Available from the AAN Web site .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site .

Patient Resources

The following is available:

- Evaluating and treating transverse myelitis. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology. 2011. 2 p. Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on April 12, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

Copyright Statement

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